CONVERSION OF ETHYL CINCHOLOIPONATE INTO A TRICYCLIC INTERMEDIATE
ADAPTABLE TO CHIRAL SYNTHESIS OF 10-DEMETHYLATED ALANGIUM ALKALOIDS

Towu Fujii,* Masashi Ohba, and Hitoshi Suzuki

Faculty of Pharmaceutical Sciences, Kanazawa University,
Takaramachi, Kanazawa 920, Japan

Abstract — The title (-)-tricyclic amino ester VII has been synthesized by means of an initial condensation of 4-benzyloxy-3-methoxyphenacyl bromide with (+)-ethyl cincholoiponate (VIII), derived from the Cinchona alkaloid cinchonine, and succeeding steps proceeding through the intermediates (+)-IX, X, XI, (-)-XIII, (-)-XIV, (+)-XV, (+)-XVI, (+)-XVII, and XVIII.

It has recently been shown in this laboratory that the Alangium alkaloid (-)-demethyltubulosine¹,² is not the 9-demethylated base (I),³ but 10-demethyltubulosine (II),⁴ whereas (+)-desmethylopisotinine, another Alangium alkaloid,² has the 9-demethyl structure (III).⁵ (-)-Demethylcephaeline is yet another alkaloid that has been assigned the alternative of the 9-demethyl (V) or the 10-demethyl structure (VI).⁶ For chiral syntheses of these 10-demethylated bases, the tricyclic amino ester VII (absolute configuration shown) would be a convenient key intermediate since the corresponding racemic form [(±)-VII] has already been converted into (+)-10-demethyltubulosine [(±)-III]⁴ and (±)-10-demethylpsychotrine [(±)-IV].⁷ We now report the first synthesis of the (-)-antipode VII, which represents an extension of our "cinchoolipon-incorporating method"⁵,⁸−¹¹ to the 10-benzyloxybenzo[a]quinolizidine series.

Treatment of (+)-ethyl cincholoiponate (VIII), prepared¹² from the Cinchona alkaloid cinchonine in 50% overall yield, with 4-benzyloxy-3-methoxyphenacyl bromide¹³ and K₂CO₃ in benzene (50−55°C, 7 h) gave the (+)-amino ketone IX [98% yield; [α]D¹⁶ +3.7° (c 2.71, EtOH)],¹⁴ which was then reduced (Na-BH₄, EtOH, 0°C, 2 h, room temp., 6 h) to afford a diastereomeric mixture of the amino alcohol X [97%; [α]D¹⁸ -1.6° (c 2.55, EtOH)]. Oxidation of the mixture X with Hg(OAc)₂-EDTA (1%aq. AcOH, reflux, 1.5 h)¹⁵,¹⁶ followed by column chromatography (silica gel or alumina, AcOEt-hexane or CHCl₃-hexane) furnished the 6-piperidone XI as a diastereomeric mixture [53% yield; [α]D²⁵ -9.6° (c 2.00, EtOH); ir (CHCl₃): 3350 (OH), 1726 (ester CO), 1618 cm⁻¹ (lactam CO)] and an oily substance [15% yield; [α]D¹⁸ +10.3° (c 2.00, EtOH); ir (CHCl₃): 3350 (OH), 1726 (ester CO), 1610 cm⁻¹ (lactam CO)] presumed⁸ to
be a diastereomeric mixture of the *cis*- and the *trans*-2-piperidones XII. On catalytic hydrogenolysis (10% Pd-C/H₂, EtOH–70% aq. HClO₄, 1 atm, 35°C, 16 h), the major product XI of the above oxidation yielded the (−)-lactam phenol XIII [99%; (α)\textsubscript{D}^25 \textsuperscript{−} \textdegree (-2.00, EtOH)], which was then hydrolyzed (2 N aq. NaOH–EtOH, 25°C, 24 h) to give the (−)-*cis*-lactam acid XIV [98%; (α)\textsubscript{D}^24 \textsuperscript{−} 0.2° (c 2.00, EtOH)].

Thermal isomerization (180°C, 1.5 h) of the (−)-*cis*-lactam acid XIV to the (+)-*trans*-lactam acid XV [74% yield; mp 122.5–123°C; (α)\textsubscript{D}^16 +68.0° (c 0.50, EtOH)] was effected in a manner similar to that\textsuperscript{5,8,9,17} described previously for structurally analogous systems. When esterified with ethanolic HCl (15°C, 24 h), (+)-XV gave the (+)-lactam ester XVI [99%; (α)\textsubscript{D}^16 +66.8° (c 0.50, EtOH)], which was benzylated (PhCH₂Br + K₂CO₃, boiling acetone, 26 h) to furnish the (+)-benzyl ether XVII [96%; (α)\textsubscript{D}^15 +55.0° (c 0.50, EtOH)]. Compound (+)-XVII was then cyclized (POCl₃, toluene, reflux, 1.5 h) and the resulting iminium salt (XVIII) was hydrogenated (Pt/H₂, EtOH, 1 atm, room temp., 1 h) to produce the desired (−)-tricyclic amino ester VII [70% overall yield from (+)-XVII; mp 99.9–99.5°C; (α)\textsubscript{D}^16 −46.0° (c 0.50, EtOH); ir (CHCl₃): 2820, 2765 (trans-quinalizidine ring), 1725 cm\textsuperscript{−} (ester CO)]. The tlc behavior and the solution ir and nmr spectra of (+)-XVI, (+)-XVII, and (−)-VII thus obtained were identical with those of the corresponding racemic variety,\textsuperscript{7} substantiating the assigned structure and stereochemistry.

In conclusion, the key intermediate (−)-VII for chiral syntheses of the 10-demethylated Alangium alkaloids has now become available through the above reaction sequence, and the synthesis of 10-demethylcephaline (VI) from (−)-VII is currently under way in our laboratory.

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REFERENCES
14. Satisfactory spectral data and/or elemental analyses were obtained for all the new compounds described.

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